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ATTI DEL CONGRESSO

ORG-PO-134 Decarboxylative Cassar-Sonogashira Coupling Reactions. Synthesis of a key intermediate of Erlotinib

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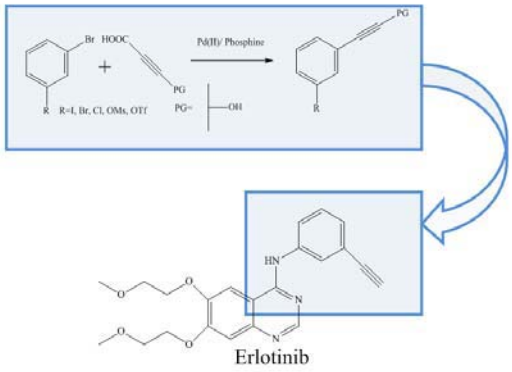
In recent years, the development of decarboxylative coupling reactions of propiolic acid derivatives on aryl halides and pseudohalides [1] emerged as a convenient approach to the synthesis of acetylenic compounds with respect to the conventional Cassar-Sonogashira coupling reaction of terminal alkynes. In the last years, several optimized protocols for decarboxylative couplings of alkynyl carboxylic acids with aryl and benzyl halides with low catalyst loading [2] and Pd-free decarboxylative cross-couplings catalyzed by copper [3] were reported. The coupling reaction of propiolic acid derivatives usually gives disubstituted symmetrical and unsymmetrical acetylenes [4], while the preparation of terminal alkynes by using this approach, at the best of our knowledge, has not been reported.



Herein, we present a protocol for the preparation of terminal alkynes from propiolic acid which was applied to the synthesis of the active pharmaceutical ingredient Erlotinib [5].

[1] Sim, S. H.; Park, H.-J.; Lee, S. I.; Chung, Y. K. *Org. Lett.*, **2008**, *10*, 433; Moon, J.; Jang, M.; Lee, S. *J. Org. Chem*. **2009**, *74*, 1403-1406; Park, J.; Park, E.; Kim, A.; Park, S. A.; Lee, Y.; Chi, K. W.; Jung, Y. H.; Kim, I. S. *J. Org. Chem*. **2011**, *76*, 2214-2219.
[2] Zhang, W. W.; Zhang, X. G.; Li, J. H. *J. Org. Chem*. **2010**, *75*, 5259-5264.
[3] Zhao, D.; Gao, C.; Su, X.; He, Y.; You, J.; Xue, Y. *Chem. Commun.* **2010**, 46, 9049-9051.
[4] Park, K; Bae, G.; Park, A.; Kim, Y; Choe, J.; Song, K. H.; Lee, S. *Tetrahedron Lett*. **2011**, *52*, 576-580; Park, K; Bae, G.; Moon, J.; Choe, J.; Song, K. H.; Lee, S. *J. Org. Chem*. **2010**, *75*, 6244-6251.
[5] The process is object of two prioritary italian patent applications MI2010A001878, MI2011A000464 and related US and EP applications.